Influence of hyperuricemia on long-term renal allograft function after renal transplantation☆

Is it a factor of chronic renal allograft dysfunction?

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Abstract

BACKGROUND: A large number of researches have confirmed that hypertension, vascular nephrosclerosis and chronic systemic inflammatorome were the importance factors of chronic allograft dysfunction. Hyperuricemia is associated with primary hypertension and vascular nephrosclerosis, and can result in chronic systemic inflammatorome, but it was uncertain whether post-transplantation hyperuricemia and its lesion influence the long term graft function.

OBJECTIVE: To investigate the prevalence of hyperuricemia in renal transplant recipients (RTRs) before and after transplantation and the influence of hyperuricemia on long term graft function.

METHODS: A total of 216 renal transplant recipients [146 males with the mean age of (40.98±11.09) years and 70 females with mean age of (40.01±11.62) years] with normal renal function after transplantation were selected from PLA Center of Kidney Transplantation and Dialysis, the 181 Hospital of Chinese PLA. In order to compare the influence of different hyperuricemia status on the long term graft function, the patients were divided into 4 groups according their pre-transplant baseline and post-transplant serum uric acid (SUA) levels, SUA normal group, pre-transplant high SUA group, post-transplant high SUA group and both pre-transplant and post-transplant high SUA group. The patients were also divided into 3 groups according to their post-transplantation SUA level to study the influence of SUA on the long term graft function, normal SUA group, hyperuricemia (SUA < 500 μmol/L) group and hyperuricemia (SUA > 500 μmol/L) group. Effects of hyperuricemia and SUA levels pre- and post-transplantation on long term graft function were observed.

RESULTS AND CONCLUSION: Hyperuricemia existed in 34.2% male RTRs and 37.7% females before transplantation, while it existed in 36.2% male RTRs and 42.4% females at the first month post-transplantation when they had normal Scr levels. The incidence rate of post-transplant hyperuricemia in female RTRs was significantly higher than male RTRs ($P < 0.05$). The average post-transplantation SUA levels in both male and female RTRs were significantly higher than those before transplantation ($P < 0.01$). At follow-up end, the pre-transplantation SUA levels did not significantly influence on the long term graft function ($P > 0.05$), meanwhile the RTRs with continuous post-transplant hyperuricimia had poorer long term graft function than those with normal post-transplantation SUA levels. It is indicated that hyperuricemia is more common in post-transplantation recipients, especially in female RTRs, when compared to pre-transplantation, and post-transplantation hyperuricemia often existed in renal transplant recipients with normal graft function. Furthermore it is suggested that post-transplantation hyperuricimia, but not pre-transplantation hyperuricemia, could also act as a factor inducing chronic renal allograft dysfunction.

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INTRODUCTION

Hyperuricemia is a common complication in renal transplant recipients (RTRs). It has been considered that soluble uric acid is an inactive substance, in physiology, and mild or moderate hyperuricemia without gout has not pathogenic effects[1]. Recently it was reported that hyperuricemia is associated with systemic hypertension and may cause the pathologic rebuild of vessels, and chronic systemic inflammatory response[2-3]. It was also reported that hyperuricemia might induce hypertrophy/hypertension, afferent arteriolar sclerosis, and accelerating the development of chronic kidney disease (CKD)[4]. However, there is much debate about whether hyperuricemia after renal transplantatation and its extent influence on long term graft function[5-6]. In this study, 216 RTRs were followed up to investigate the influence of incidence and extent of hyperuricemia in RTRs before and after renal transplantation on long term graft function (eGFR).

SUBJECT AND METHODS

Design

Retrospectively clinical observation and grouping contrast study.

Time and setting

This study was performed at PLA Center of Kidney Transplantation and Dialysis, the 181 Hospital of Chinese PLA from January 2003 to December 2005.

Subjects

A total of 216 RTRs, 146 males (67.6%) with a mean age of (40.98±11.09) years and 70 females (32.4%) with a mean age of (40.01±11.62) years, which received renal allografts in our transplant center from January 2003 to December 2005 and had normal or recovered allograft function (SCr < 130 μmol/L more than one month). The patients who lost to follow-up, with abnormal graft function and with primary disease of diabetes or hyperuricemia were excluded.

Hyperuricemia was diagnosed with an increased serum uric acid (SUA) more than 420 μmol/L in males and 380 μmol/L in females. The renal allograft function was determined using SCr level. The average serum uric acid value of each RTRs, during their long term follow-up, was calculated. The patients were treated with Cyclosporin + Mizoribine (5-Hydroxy-1-beta-D-ribofuranosyl-1H-imidazole-4-carboxamide) + Prednisone. The mean SUA level at each time point during follow-up was calculated. The patients were followed-up in schedule made before they were discharged: followed up at half-month, one-month, two-month, three-month and six-month intervals respectively, in the patients within 3 months, 3-6 months, 6–12 months, 12–24 months and over 24 months after transplantation. There were 34, 42 and 140 patients been followed-up for one year, 2 years and over 3 years respectively.
In order to evaluate the influence of SUA, increased before or after renal transplantation, on long term graft function, all 216 recipients were divided into four groups: group A (n=84) with normal pre- and post-transplant SUA levels, group B (n=45) with pre-transplant hyperuricemia but normal post-transplant SUA levels, group C (n=58) with normal pre-transplant SUA levels but post-transplant hyperuricemia, and group D (n=29) with both pre- and post-transplant hyperuricemia.
In order to compare the influences of post-transplant SUA levels increased to different degrees on long term graft function, all the recipients were divided into three groups: group 1 (n=129) with normal post-transplant SUA levels, group 2 (n=46) with post-transplant hyperuricemia at a level < 500 μmol/L, and group 3 (n=41) with post-transplant hyperuricemia at a level > 500 μmol/L.

Main outcome measures

SUA level, Scr level and eGFR.

Statistical analysis

The data were expressed as Mean ± SD unless indicated otherwise. SPSS 10.0 (SPSS Inc., Chicago, IL, USA) software was used. Univariate analysis was used for groups' variables and Chi-square test was used for comparison of frequencies of hyperuricemia. P value of < 0.05 was considered significant.

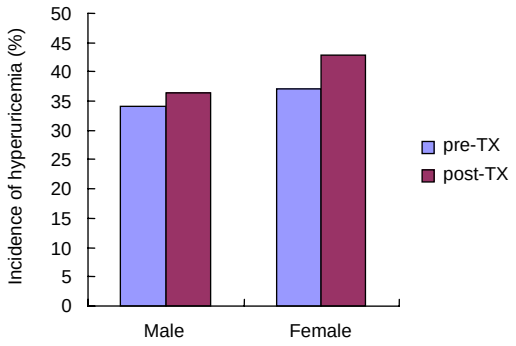
RESULTS

Quantitative analysis of the participants

There were 342 patients received renal transplantation in our transplant center during the three years. A total of 216 patients with normal graft function after transplantation and without diabetes or primary hyperuricemia were included, 34 patients underwent a follow-up for 1 year, 42 for 2 years, and 140 for 3 years.

Incidence of hyperuricemia in RTRs before and after transplantation

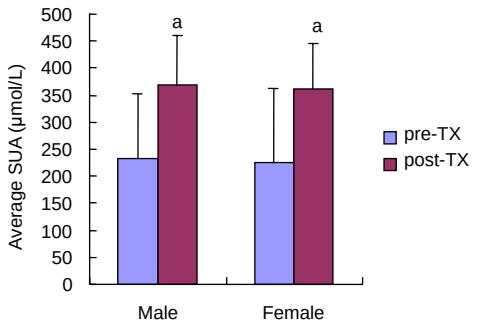
Hyperuricemia existed in 34.2% male RTRs and 37.7% females before transplantation, while existed in 36.2% male RTRs and 42.4% female at the first month after renal transplantation when they had normal serum creatinine levels (SCr). The incidence rates were not significantly different between pre-transplant and post-transplant hyperuricimia in either male or female RTRs (P>0.05, Figure 1).



pre-TX: before transplantation; post-TX: after transplantation

Figure 1 Incidence of hyperuricemia in renal transplant recipients before and after transplantation

The incidence rate of post-transplant hyperuricemia in female RTRs was significant higher than male RTRs (P < 0.05), but the average post-transplant SUA levels in male RTRs were slightly than females (P > 0.05). The average post-transplantation SUA levels in either male or female RTRs were significantly higher than those before transplantation (P < 0.01, Figure 2).

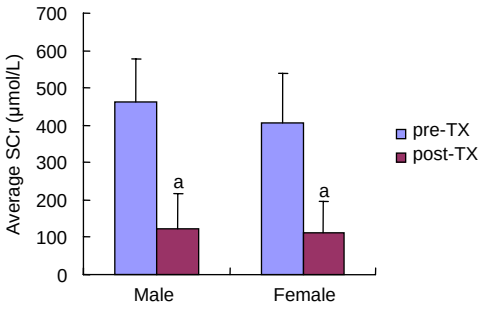


[a]P < 0.01, *vs.* pre-tx

pre-TX: before transplantation; post-TX: after transplantation

Figure 2 Average serum uric acid (SUA) level in renal transplant recipients before and after

The average SCr levels of male and female RTRs before and after transplantation were shown in Figure 3.



[a]P < 0.01, *vs.* pre-tx

pre-TX: before transplantation; post-TX: after transplantation

Figure 3 Average serum creatinine (SCr) level in renal transplant recipients before and after

Influence of pre- and post-transplant hyperuricemia on long term graft function (Table 1)

Table 1 Influence of hyperuricemia pre- and post-transplantation on long term graft function (eGFR) ($\bar{x}$±s, mL/min)

Group	*n*	1-mon eGFR	12-mon eGFR	24-mon eGFR	36-mon eGFR
A	84	58.81±26.65	59.33±26.73	52.63±23.72	46.59±23.21
B	45	60.91±32.44	55.80±24.90	49.92±21.73	43.95±22.59
C	58	63.21±33.95	44.36±19.67^{bd}	37.38±16.60^{bd}	29.99±13.05^{bd}
D	29	59.41±26.77	35.20±14.44^{ac}	30.45±12.67^{ac}	19.48±7.25^{ac}

Group A: patients with normal pre- and post-transplant serum uric acid (SUA) levels; Group B: patients with pre-transplant hyperuricemia but normal post-transplant SUA levels; Group C: patients with normal pre-transplant SUA levels but post-transplant hyperuricemia; Group D: patients with both pre- and post-transplant hyperuricemia; $^{a}P < 0.01$, $^{b}P < 0.05$, *vs*. group A; $^{c}P < 0.01$, $^{d}P < 0.05$, *vs*. group B

At the end of 3 years follow up, the eGFR of group A with normal pre- and post-transplant SUA levels was not significantly different from group B with pre-transplant hyperuricemia but normal post-transplant SUA, and was significantly higher than group C with normal pre-transplant SUA levels but post-transplant hyperuricemia and group D with both pre- and post-transplant hyperuricemia ($P < 0.05$ and $P < 0.01$ respectively).

At the end of 3 years follow up, the eGFR of group C with normal pre-transplant SUA levels but post-transplant hyperuricemia was significant lower when compared to group B with pre-transplant hyperuricemia but normal post-transplant SUA ($P < 0.05$).

At the end of 3 years follow up, the eGFR of group D with both pre- and post-transplant hyperuricemia was significantly lower, compared to group B with pre-transplant hyperuricemia but normal post-transplant SUA ($P < 0.01$), but not significantly lower when compared to group C with normal pre-transplant SUA levels but post-transplant hyperuricemia ($P > 0.05$).

Influence of SUA levels on long term graft function (Table 2)

Table 2 Influence of serum uric acid (SUA) levels on long term graft function (eGFR) ($\bar{x}$±s, mL/min)

Group	*n*	1-mon eGFR	12-mon eGFR	24-mon eGFR	36-mon eGFR
1	129	64.03±31.87	61.10±28.49	52.87±24.27	46.71±21.13
2	46	61.10±32.63	43.51±17.37^{b}	38.27±16.32.53^{a}	30.36±11.51^{a}
3	41	59.89±30.63	24.22±11.14^{ac}	19.88±8.63^{ac}	16.46±6.25^{ac}

Group 1: patients with normal post-transplant SUA levels; Group 2: patients with post-transplant hyperuricemia at a level < 500 μmol/L; Group 3: patients with post-transplant hyperuricemia at a level > 500 μmol/L; $^{a}P < 0.01$, $^{b}P < 0.05$, *vs*. group 1; $^{c}P < 0.01$, *vs*. group 2

The baseline renal allograft function (eGFR one month after transplantation) was not significantly different in all groups. At the end of 3 years follow up, the average eGFR in group 3 with post-transplant hyperuricemia at a level > 500 μmol/L was significantly lower than either group 2 with post-transplant hyperuricemia at a level < 500 μmol/L or group 1 with normal post-transplant SUA level ($P < 0.01$). The average eGFR in group 2 with post-transplant hyperuricemia at a level < 500 μmol/L was significantly lower than group 1 with normal post-transplant SUA levels ($P < 0.05$).

DISCUSSION

Although many new immunodepressants have been continuously emerging, and renal transplant technique has been progressed much more than before, the long term outcome of RTRs was still not optimistic. Both immune and no-immune factors influence on the long term outcome of the RTRs[7]. This study showed that there was a high incidence of hyperuricemia in despite of the RTRs with normal graft function. The incidence rate of hyperuricemia in female RTRs was higher than male RTRs. Meanwhile by long term follow-up, the study also shown that SCr level is significantly higher in RTRs with persistent post-transplant hyperuricemia, than those with a normal level of post-transplant SUA. Furthermore it is suggested that post-transplant hyperuricimia, but not pre-transplant hyperuricemia, would be a factor inducing chronic renal allograft dysfunction. Min *et al*[5] reported that early-onset moderate-to-severe hyperuricaemia was found to be a significant risk factor for chronic allograft nephropathy and a poorer graft survival. Even after control of the baseline graft function, hyperuricaemia was also found to be a marker of long-term graft dysfunction and failure. The impact of moderate-to-severe hyperuricaemia on renal transplant survival was dependent on the duration of exposure.

The fact is well known that post-transplantation hyperuricemia is closely associated with insufficient renal function[8]. The RTRs with abnormal graft function were excluded in our study just as in our study, so their high level of SUA obviously not due to poor graft function. Furthermore analyses of the clinical data of the recipients transplanted in our center shown that the main primary diseases causing their chronic renal failure before the transplantation were glomerulonephritis (60.6%), tubulointerstitial nephropathies (24.2%), hypertension-associated renal disease (6.9%) and diabetic nephropathy (5.6%), but only 2.7% of them with primary hyperuricemia. It demonstrated that the main cause of post-transplant hyperuricemia of RTRs in was not primary hyperuricemia. According to literature, therapies with immunosuppressive agents including cyclosporine[9], mizoribine[10] and glucocorticoids many cause post-transplant hyperuricemia. Additional risk factors include diuretic therapy, male RTRs, elder RTRs, graft dysfunction and obesity [3, 11]. Diet may be one of the important factors inducing post-transplant hyperuricemia. Improvement of internal environment of RTRs improves their appetite after transplantation, and improved appetite and the ignoring of diet restriction often result in the increasing of SUA. The patients in our study were treated mainly on cyclosporine, mizoribine and different dosage of glucocorticoids.

It had been reported that gout in renal allograft recipients was associated to the pretransplant hyperuricemic status[12]. But some of RTRs in our study with normal SUA before transplantation developed hyperuricemia after transplantation. Adequate dialysis before transplantation can keep a lower prevalence of hyperuricemian than after transplantation. 184 of the 216 patients were dialyzed 12 hours a week and only 32 of the 216 patients were dialyzed 8 hours a week. Cohen *et al*[13] reported that the incidence of gout in patients with ESRD may be similar to that of general medical populations, with a 5%

incidence of gout after 1 year on dialysis and 15.4% incidence after 5 years, the incidence of gout in the predialysis patients or RTRs was higher than that in maintenance dialysis patients. As we have known, the incidence of primary hyperuricemia is more common in males than in females. Research from China reported that hyperuricemia was significantly more prevalent in men than in women (32.1% *vs*. 21.8%)[14]. But our data showed that the incidence rate of post-transplant hyperuricemia was higher in female RTRs than that in male RTRs, due to the different diagnosis standard. But the average SUA level was lower in female RTRs, compared to male RTRs, which is to say, hyperuricemia in female RTRs was not more serious than male RTRs.

Previously it was considered that soluble uric acid was an inactive substance in physiology and mild or moderate hyperuricemia without gout was not a pathopoiesis factor of chronic kidney disease as well as other important disorders[1]. Now our results showed that the eGFR in RTRs with mildly elevated SUA levels (< 500 μmol/L) was significantly lower than RTRs with normal average SUA levels at the end of 36 months follow-up. It is suggested that continuous elevation of post-transplant SUA levels may damage long-term graft function. Recent clinical and epidemiological studies have found that hyperuricemian could induce pathological restructure of vessels and vascular nephrosclerosis, and was associated with the mortality and development of hypertension[15-16], cardiovascular diseases and chronic renal diseases[2, 17-18]. It has been reported recently that soluble uric acid has important biologic roles such as pro-inflammatory and proliferative effects on vascular smooth muscle cells, induction of the dysfunction of endothelial cells in rats[19], and hyperuricemia may induce systemic inflammatorome and generation of oxidative stress[17]. In the other hand, there are vast evidences proving that hypertension, vascular nephrosclerosis, and systemic inflammatorome are important factors inducing chronic graft dysfunction[20]. Uric acid can elevate the immune response[21], by stimulating dendritic cell maturation and enhancing T-cell responses to foreign antigens[22]. These research results may explain the discovery in the study.

Associations between SUA levels and metabolic syndrome (MS) have been reported, that men with high SUA concentrations had a 1.60-fold increase in risk of MS as compared with those who had low SUA concentrations. Among women, the risk of MetS was at least 2-fold higher for high SUA concentrations[23]. Many authors suggested that hyperuricemia is a composite of MS[24-25]. Our transplant team had found that insulin resistance and MS after renal transplantation also played an important role on long term allograft outcome[26]. Hyperuricemia may be a risk factor of insulin resistance[27].

Several reasons made these patients SUA level elevated for a long time and exactly because the long time high levels of SUA deteriorated their graft function[5]. Due to considerate of the adverse effect of allopurinol or asymptomatic hyperuricemia can be ignored[28]. Allopurinol was not used in these patients except SUA was extremely high. In patients with primary hyperlipidemia, atorvastatin but not simvastatin, has been shown to be able to reduce SUA concentrations[29], while patients with postoperative hyperlipidemia in the study were treated with simvastatin but not atorvastatin. Another measure to abate the affection of hyperuricemia was using an angiotensin II receptor antagonist, Losartan, which has been reported to have a uricosuric effect[30] and it was rarely used in our patients too. This condition may explain why the long term graft function of our patients was affected more by post-transplantation hyperuricemia than in other researches. The results of the study also suggested that effective prevention and treatment of hyperuricemia in RTRs would be important in protection of graft function, and also reduce all-cause mortality and cardiovascular mortality in patients with CKD[9, 31].

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肾移植后高尿酸血症与移植肾的远期功能：是慢性移植肾功能丢失的因素吗？☆

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摘要

背景：大量研究充分证实高血压、血管性肾硬化、慢性全身炎症反应都是移植肾慢性失功的重要诱因。高尿酸血症与原发性高血压及血管性肾硬化有关，并且可引起全身炎症反应，那么肾移植后高尿酸血症发病及病变程度是否对移植肾远期功能有影响呢？

目的：实验首次探讨肾移植前后高尿酸血症及其病变程度对移植肾远期功能的影响。

方法：选择解放军第一八一医院全军肾移植与透析治疗中心肾移植后肾功能恢复正常患者 216 例，男性 146 例，年龄(40.98±11.09) 岁；女性 70 例，年龄(40.01±11.62)岁。为比较移植前后高尿酸血症对移植肾远期功能的影响，将病例分为 4 组：正常组、移植前高尿酸血症组、移植后高尿酸血症组、移植前后均高组。为比较移植后不同血清尿酸水平对移植肾远期功能的影响，将病例分为 3 组：血尿酸水平正常组、血尿酸水平高于正常但<500 μmol/L 组、血尿酸水平> 500 μmol/L 组。观察移植前后高尿酸血症对移植肾远期功能的影响；移植后不同程度增高血尿酸水平对移植肾远期功能的影响。

结果与结论：移植前男性患者高尿酸血症患病率为 34.2%，女性患者为 37.7%；移植后 30 d 肾功能恢复正常时，男性患者高尿酸血症患病率为 36.2%，女性患者为 42.4%，与移植前相比差异均无显著性意义。女性患者肾移植后高尿酸血症患病率高于男性患者($P < 0.05$)。男女患者移植后血尿酸水平均高于移植前($P < 0.01$)。随访 3 年时，移植前血尿酸水平对患者远期血肌酐水平无显著影响($P > 0.05$)，但移植后血尿酸水平持续增高者，远期血肌酐水平显著高于移植后血尿酸水平正常者。实验结果显示，肾移植后肾功能恢复良好患者的高尿酸血症患病率及程度均高于移植前，尤其是在女性患者。移植后尿酸持续增高患者远期移植肾功能不如移植后尿酸正常患者，提示移植后高尿酸血症可能是导致慢性移植肾失功的因素之一。

关键词：肾移植；高尿酸血症；慢性移植肾失功

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